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Sinoatrial Function After Cardiac Transplantation

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The function of both the denervated donor and innervated recipient sinus nodes of 14 asymptomatic cardiac transplant recipients was assessed. Tests of sinoatrial function were performed in 14 donor and 10 recipient atria. The mean spontaneous cycle length of the recipient atria was significantly longer than that of the donor atria (944 ± 246 versus 663 ± 158 ms, $p < 0.01$). Donor sinus node recovery time was prolonged in four patients (> 2,500 ms in two) and recipient recovery time was prolonged in six patients. In those patients with normal sinus node function tests, the recovery time of the recipient sinus node was longer than that of the donor sinus node (1,170 ± 207 versus 864 ± 175 ms, $p < 0.02$). The pattern of response of recovery times to increasing pacing rate was predictable and organized in the donor but chaotic in the recipient, and the longest sinus node recovery time occurred at the shortest pacing cycle length used in 12 of the 14 donor atria but in only 1 of the 10 recipient atria ($p < 0.001$). Secondary pauses occurred in none of the normal donor atria and in all of the abnormal donor atria ($p < 0.001$); however, they occurred in both normal and abnormal recipient atria.

The recipient and donor atria were paced alone and synchronously in the same patients. Synchronous pacing had no effect on the recovery times of the donor sinus node but significantly lengthened those of the recipient (sinus node recovery time: 1,266 ± 218 to 1,547 ± 332 ms, $p < 0.02$; corrected recovery time: 322 ± 102 to 686 ± 188 ms, $p < 0.01$). In the donor atria, abnormal recovery time was invariably associated with abnormal sinoatrial conduction time. There was a strong correlation between sinoatrial conduction time measured by the methods of Strauss and Narula and their coworkers in the donor atria ($r = 0.98$, $p < 0.001$) but not in the recipient atria ($r = 0.72$).

In the absence of autonomic influences, tests of sinus node function of the donor atria produce predictable and consistent results and, therefore, may be more clinically reliable than in intact human subjects. There is a high incidence of recipient sinus node dysfunction in asymptomatic long-term survivors of cardiac transplantation.

During the surgical procedure currently used for clinical human cardiac transplantation (1,2), the posterior portions of the recipient right and left atria are left in situ, with the sinus node and its neural connections undisturbed. This technique avoids the need for difficult multiple venous anastomoses. All incisions, ligatures and sutures in the donor atrium are fashioned in such a way as to avoid trauma to the donor sinus node and muscular tracts (3). Each patient thus has two sinus nodes—the recipient sinus node driving only the atrial remnants and the donor sinus node driving the donor atria and ventricles. Despite losing its native blood supply, the recipient sinus node usually remains viable, presumably through bronchial collateral vessels (4), and remains functionally innervated responding appropriately to physiologic stimuli (5,6). The transplanted donor heart, however, appears to remain both anatomically and functionally denervated indefinitely (5–8). The two sets of atria beat totally independently and electrical activity from both recipient and donor atria may be recorded on the surface electrocardiogram (5,6) and from intracardiac electrodes (9,10). Similarly the two sets of atria may be paced independently (11).

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The autonomic nervous system may significantly alter sinus node function (12,13) and thus reduce the sensitivity and specificity of formal electrophysiologic testing of sinus node function (14,15). Attempts have been made to overcome this problem with pharmacologic autonomic blockade, using the technique of Jose (16) to assess "intrinsic" sinus node function (17–21). This technique may, however, have certain methodologic problems. The pharmacologic agents used may result in alterations in hemodynamic status, the competitive blockade may not be complete and beta-receptor blocking agents may possess direct membrane effects separate from their autonomic effects (22,23).

In the unique situation occurring after cardiac transplantation, sinus node function of both the innervated and denervated sinus nodes in the same patient may be assessed under the same humoral and, to a certain extent, hemodynamic influences. Although certain aspects of sinoatrial function in transplant patients have previously been investigated, in particular the effect of overdrive suppression and of digoxin (24), a detailed systematic evaluation of recipient and donor sinus node function in relatively long-term survivors of cardiac transplantation has not been reported. The purpose of this study is to perform such an evaluation. The study also helps clarify the effect of autonomic influences on conventional invasive tests of sinus node function and the values and limitations of such testing.

Methods

Patients. Fourteen cardiac transplant recipients underwent routine electrophysiologic evaluation 4 to 28 months (mean 14) after transplantation. Their ages ranged from 24 to 54 years (mean 38.5) and 13 patients were male. This group consisted of all patients in the Papworth Hospital transplantation series who had survived at least 4 months at the time this investigation was performed. The donor hearts had been taken from patients whose ages ranged from 16 to 29 years (mean 20) (Table 1). The study was performed because of the reported high incidence of sinus node and conduction system disease in patients after cardiac transplantation (8,25,26).

At the time of investigation all patients were functionally well with no clinical, biochemical or electrocardiographic evidence of rejection. Two patients had complete right bundle branch block on their rest electrocardiogram, but in one of these cases this abnormality had been present on the donor electrocardiogram before transplantation. The remaining patients all had normal electrocardiograms apart from the presence of independent recipient P waves. All patients were taking prednisolone and azathioprine as routine immunosuppressive therapy. No patient was taking cardioactive drugs.

Electrophysiologic study. All patients were studied in the nonsedated, postabsorptive state after written informed consent had been given. This study was performed as part of a more extensive electrophysiologic evaluation for which approval had been granted by the Ethical Committee of St. Bartholomew's Hospital and reapproved after review of the first eight cases.

Table 1. Individual Patient Data

Case*	Age (yr) & Sex	Pre-Transplant Diagnosis	Time of Study (months postop)	Age of Donor (yr)
2	54M	IHD	28	21
3	31M	IHD	22	17
4	37M	CM	18	16
6	24M	CM	17	22
10	24M	CM	14	16
12	44M	IHD	11	20
13	41M	CM	9	19
16	49M	IHD	18	21
17	43M	IHD	4	19
18	35M	IHD	17	25
19	53M	IHD	15	18
20	28M	IHD	14	25
22	34F	CM	8	29
29	42M	IHD	7	18

*Case numbers refer to the number currently in Papworth Hospital transplantation series. CM = cardiomyopathy; F = female; IHD = ischemic heart disease; M = male; postop = postoperative.

Using local anesthesia and fluoroscopic guidance, five pacing electrodes were introduced through the right femoral vein and positioned in the heart. A quadripolar electrode was positioned at the superior vena cava-right atrial junction to record and stimulate the recipient atrium. Lateral fluoroscopy was used to confirm the posterior position of this electrode. The distal two poles were used for stimulation and the proximal poles for recording. Two bipolar electrodes were positioned in the "appendage" of the donor right atrium for recording and stimulation, respectively. The anterior position of these electrodes was confirmed radiographically. An electrode was also manipulated across the septal leaflet of the tricuspid valve to record the His potential and a further electrode advanced to the apex of the right ventricle for stimulation.

Bipolar endocardial signals from each recording electrode were passed through appropriate amplification and filtering (high pass = 50 Hz, low pass = 500 Hz) and recorded on a Mingograf (Siemens-Elema, Stockholm, Sweden) ink jet recorder at a paper speed of 100 mm/s, simultaneously with four surface electrocardiographic leads (to provide a roughly orthogonal representation of the electrocardiogram).

Intracardiac stimulation was achieved with a Devices 4279 isolated "Neurolog" stimulator (Digitimer Ltd., Welwyn, England). Constant voltage, current-limited square wave pulses of 1.5 to 2.5 ms duration were delivered at approximately twice the diastolic threshold.

Methods of evaluation and definitions. *Sinus cycle length* was defined as the average cycle length of 10 consecutive, spontaneous sinus cycles. The cycle length of both the donor and recipient atria were measured.

Sinus node recovery time: This was the maximal sinus pause after the termination of right atrial pacing at rates of 110 (if appropriate), 130, 150 and 170 beats/min for periods of 15, 30 and 60 seconds, measured from the last pacing stimulus to the first high frequency deflection of the first sinus escape beat (27,28). The results were corrected by subtraction of sinus cycle length (corrected sinus node recovery time) (29). The upper limit of normal for sinus node recovery time was accepted as 1,400 ms (30) and for corrected sinus node recovery time as 525 ms (29). Both donor and recipient recovery times were assessed in all patients using synchronous pacing of both atria. In six donor atria and six recipient atria, a comparison was made between recovery times obtained during pacing of the atria alone and those obtained during synchronous pacing of both atria.

Subsequent post-pacing cycles from 2 to 10 were recorded to observe secondary pauses, which were defined as any cycle during cycles 3 to 10 that was longer than the primary recovery cycle (31).

Sinoatrial conduction time (method of Strauss et al. [31,32]): During sinus rhythm, premature atrial stimuli were introduced after every eighth beat at gradually decreasing coupling intervals (20 to 40 ms decrements, depending on original cycle length) until atrial refractoriness was encountered. The following four consecutive sinus intervals were measured:

A_1-A_1 interval = the spontaneous cycle length immediately preceding the extrastimulus.
A_1-A_2 interval = the coupling interval of the extrastimulus.
A_2-A_3 interval = the post extrastimulus pause.
A_3-A_4 interval = the post return cycle, that is, the next interval after A_2-A_3.

The values of A_1-A_2, A_2-A_3 and A_3-A_4 were normalized, that is, expressed as a percent of the spontaneous sinus cycle length (A_1-A_1). The normalized values of A_2-A_3 and of A_3-A_4 were plotted against normalized values of A_1-A_2. A second graph was also constructed plotting normalized A_2-A_3 minus the interval by which A_3-A_4 exceeds A_1-A_1 against normalized A_1-A_2 to calculate "corrected" sinoatrial conduction time.

Changes in sinus node automaticity after atrial extrastimulation have been recognized in studies in isolated rabbit atrial preparations (33–35), and it has been stated that prolongation of the A_3-A_4 cycle can be used to monitor the degree of this sinus node suppression (36). The prolongation of A_3-A_4 may, however, also be the result of a shift of pacemaker after A_2 (34,37), although this may similarly be purely an expression of depressed sinus node automaticity. It has been suggested that "correction" of the sinoatrial conduction time, as just described, may take account of the possible error in the calculation induced by sinus node suppression (31,38).

Sinoatrial conduction time was determined from the cluster of points on the plateau of the graph (zone of reset). Calculations were made from those points that fell closest to the zone of nonreset (32). Using these points the total sinoatrial conduction time (retrograde and anterograde) was calculated by subtracting A_1-A_1 from A_2-A_3. Since sinoatrial conduction into and out of the node may not be equal (34,35), this value was not divided by two. The sinoatrial conduction time, using Strauss' method, of both donor and recipient atria was assessed in all patients.

Sinoatrial conduction time (method of Narula et al. [39]): This determination was performed by pacing the right atrium slightly faster (5 to 10 beats/min) than the sinus rate for eight cycles. The interval from the last paced atrial electrogram to the next spontaneous sinus discharge represents the sinus cycle length plus retrograde conduction into, and anterograde conduction out of, the sinus node. Sinoatrial conduction time was calculated by subtracting sinus cycle length from the first return cycle. This method was repeated eight times in each patient and the longest and mean values were recorded. Sinoatrial conduction times using the method of Narula et al. (39) were assessed in six donor atria and four recipient atria. The upper limit of normal for sinoatrial conduction time by either method (Strauss et al. or Narula et al.) was taken as 206 ms (39,40).

Expected intrinsic heart rates (IHR) of the donor atria were calculated from the age of the donor heart (Table 1) using the linear regression equation of Jose and Collison (41):

$$\text{IHR} = 118.1 - (0.57 \times \text{age}).$$

The 95% confidence limits for patients aged less than 45 years is IHR ± 14%.

Statistical analysis. All values are quoted as the mean ± 1 standard deviation. Comparisons of data were made using the Student's two-tailed *t* test for paired and nonpaired data. Differences were considered significant when the probability (p) value was less than 0.05. When a correlation between two variables was sought, least squares linear regression analysis was used and the correlation coefficient (r) value and p value calculated. Incidence rates were compared by chi-square analysis and the p value calculated.

Results

In two patients, no electrical activity of the recipient atrium could be detected despite extensive and careful mapping of the whole of the posterior atrial wall; neither could this atrium be paced. In one patient, the recipient atrium was fibrillating and in one additional patient, the recipient and donor atria remained synchronized during a variety of physiologic and pacing maneuvers. Under no circumstance

did the two atria beat independently, the donor atrium controlling the rate of the recipient at all times. Data on this patient have been reported in detail elsewhere (42). No other patient demonstrated synchronization of the donor and recipient atria at any time during the period of this investigation. Therefore, this report describes in detail the results obtained from 14 donor atria and 10 recipient atria.

Sinus Node Recovery Time

Donor versus recipient atria. The mean spontaneous sinus cycle length of the recipient atria was significantly longer than that of the donor atria (944 ± 246 versus 663 ± 158 ms, $p < 0.01$). The donor sinus node recovery time, assessed during combined pacing of both sets of atria, ranged from 665 to 2,580 ms (mean 1,212 ± 650) and the corrected recovery time from 135 to 1,440 ms (mean 500 ± 448). The recipient sinus node recovery time ranged from 900 to 2,155 ms (mean 1,432 ± 335) and the corrected recovery time from 245 to 910 ms (mean 581 ± 209) (Tables 2 and 3). The recovery time of the donor sinus node was prolonged in 4 (of the 14) patients and of the recipient sinus node in 6 (of the 10) patients. In the donor atria, there was a very good correlation between sinus cycle length at rest and both sinus node recovery time ($r = 0.95$, $p < 0.001$) and corrected recovery time ($r = 0.93$, $p < 0.001$). The correlation was less strong in the recipient atria (sinus node recovery time: $r = 0.87$; corrected recovery time: $r = 0.59$).

Effect of increasing pacing rate. In those patients with normal function of both sinus nodes, as assessed by overdrive suppression during combined pacing of both sets of atria, the sinus node recovery time (1,170 ± 207 versus 864 ± 175 ms, $p < 0.02$) and corrected recovery time (403 ± 106 versus 258 ± 103 ms, $p < 0.05$) of the recipient were longer than those of the donor. In these patients with normal sinus node function, the pattern of response of both the uncorrected and corrected recovery times to progressively more rapid pacing rates was organized and predictable in the donor atria, increasing progressively with faster pacing rates, but "chaotic" in the recipient, with a tendency to shorten at faster pacing rates (Fig. 1). The pattern of response in the patients with abnormal donor sinus node function was less predictable, but still tended to increase with faster pacing rates. The longest sinus node recovery time occurred at the shortest cycle length of the pacing cycle lengths used (350 ms) in 12 of the 14 donor atria, but in only 1 of the 10 recipient atria ($p < 0.001$) (Fig. 2). The cycle length resulting in the longest sinus node recovery time was 366 ± 40 ms in the donor atria and 448 ± 63 ms in the recipient ($p < 0.001$) (Fig. 2). The same relation was also apparent for both normal and abnormal sinus nodes when analyzed separately.

Effect of increasing pacing duration. Similarly, there were differences in the responses of the two sets of atria to increasing pacing duration. In the donor atria overall, corrected sinus node recovery time was longer with longer durations of pacing, although the pattern was not as clear as with increasing pacing rate (15 seconds: 239 ± 93 ms; 30 seconds: 365 ± 399 ms, $p < 0.05$; 60 seconds: 329 ± 362 ms). In the patients with normal donor sinus node function, however, corrected recovery time shortened with increasing pacing duration (15 seconds: 204 ± 74 ms; 30 seconds: 189 ± 87 ms; 60 seconds: 166 ± 117 ms, $p < 0.05$), whereas it was markedly longer after the two pacing periods with the longer durations in the patients with abnormal donor sinus node function (15 seconds: 352 ± 43 ms; 30 seconds: 937 ± 484 ms, $p < 0.01$; 60 seconds: 858 ± 387 ms, $p < 0.01$) (Fig. 3). In the recipient atria there was no significant change except for a slight increase in recovery time after pacing for 30 seconds in those patients with abnormal recipient sinus node function (Fig. 3).

Secondary pauses. These occurred in none of the patients with normal donor sinus node function and in all of the patients with abnormal function ($p < 0.001$). In the

Table 2. Overall Results of Sinus Node Function Tests

	Donor	Recipient	Significance (p value)
Mean SCL	663 ± 158	944 ± 246	<0.01
SNRT (all patients)	1,212 ± 650	1,432 ± 335	NS
cSNRT (all patients)	500 ± 448	581 ± 209	NS
SNRT (normal patients)	864 ± 175	1,170 ± 207	<0.02
cSNRT (normal patients)	258 ± 103	403 ± 106	<0.05
PCL producing SNRTmax	366 ± 40	448 ± 63	<0.001
SNRTmax at PCL 350 ms	86%	10%	<0.001
Secondary pauses (normal patients)	0%	50%	<0.02
Secondary pauses (abnormal patients)	100%	66%	NS
SACT (Strauss)	179 ± 101	180 ± 67	NS

All values are expressed in milliseconds as the mean ± 1 standard deviation (SD). cSNRT = corrected sinus node recovery time; max = maximal; NS = not significant; PCL = pacing cycle length; SACT = sinoatrial conduction time; SCL = sinus cycle length; SNRT = sinus node recovery time; Strauss = method of Strauss et al. (31,32).

Table 3. Individual Patient Results of Sinus Node Function Tests

	Donor					Recipient				
Case	SCL	SNRT	cSNRT	SACT(1)	SACT(2)	SCL	SNRT	cSNRT	SACT(1)	SACT(2)
2	910	2580	1440	220	214	860	1315	560	234	196
3	580	925	285	240	235	1170	1430	530	51	125
4	520	665	135	103	101	940	1400	440	235	210
6	660	1235	465	177	138	700	1160	455	148	133
10	535	820	250	110	93	1010	1580	555	125	119
12	520	755	230	150	150	655	900	245	157	159
13	660	920	290	183	181	—	—	—	—	—
16	515	740	200	179	139	1050	1620	910	157	154
17	585	770	175	120	120	—	—	—	—	—
18	570	745	170	153	148	—	—	—	—	—
19	690	1065	385	199	173	—	—	—	—	—
20	790	1455	685	460	275	1470	2155	855	192	191
22	1040	2550	1360	206	204	820	1220	470	222	209
29	710	1740	935	5	0	760	1540	790	282	273

All values are in milliseconds. cSNRT = corrected sinus node recovery time; SACT(1) = sinoatrial conduction time (Strauss); SACT(2) = "corrected" sinoatrial conduction time (Strauss); SCL = sinus cycle length; SNRT = sinus node recovery time.

recipient atria, secondary pauses occurred in 50% of patients with normal and 66% of those with abnormal sinus node function (difference not significant [NS]). Analysis of all the pacing interventions revealed that secondary pauses occurred in none of the pacing sequences in the donor atria of patients with normal function but in 35% of the sequences in those of patients with abnormal function ($p < 0.0001$). In the recipient atria, secondary pauses occurred in 11% of sequences in patients with normal function and 19% of sequences in those with abnormal function (NS).

Heart rate and mode of pacing. Calculation of expected intrinsic heart rate from the age of the donor heart, using the linear regression equation derived by Jose and Collison (41), revealed that a donor heart rate more than 2 standard deviations below the calculated rate was almost invariably associated with abnormal donor sinus node function tests (Table 4).

To assess the possible effect of hemodynamic or mechanical influences, or both, on the sinus node recovery time, recovery times in six patients were measured during pacing of the donor or recipient atrium alone and then again during synchronous pacing of both sets of atria. The mode of pacing had no effect on either sinus node recovery time (1,082 ± 586 versus 1,163 ± 721 ms, NS) or corrected recovery time (403 ± 379 versus 467 ± 489 ms, NS) in the donor. In the recipient, however, synchronous pacing significantly lengthened recovery times (sinus node recovery time: 1,266 ± 218 to 1,547 ± 332 ms, $p < 0.02$; corrected recovery time: 322 ± 102 to 686 ± 188 ms, $p < 0.01$) (Fig. 4 and 5).

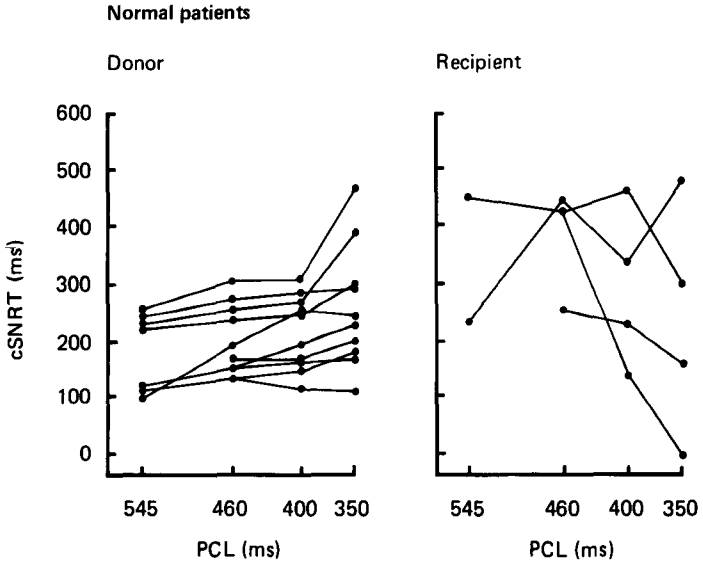


Figure 1. Effect of pacing rate on corrected sinus node recovery time (cSNRT) in individual donor and recipient atria in patients with normal sinus node function tests. PCL = pacing cycle length.

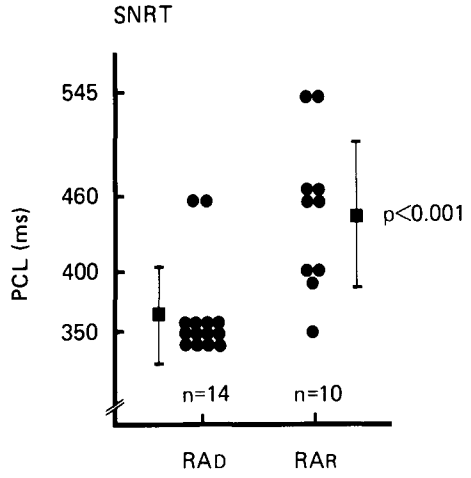


Figure 2. Frequency at which maximal sinus node recovery time (SNRT) occurred in the donor and recipient atria at the various pacing cycle lengths (PCL). The mean cycle length (± 1 standard deviation) resulting in the longest sinus node recovery time is also indicated. RAD = donor right atrium; RAR = recipient right atrium.

Sinoatrial Conduction Time

Relation to donor sinus node recovery time. Sinoatrial conduction times, using the method of Strauss (31,32), were assessed in all patients. Values ranged from 5 to 460 ms (mean 179 ± 101) in the donor and from 51 to 282 ms (mean 180 ± 67) in the recipient. After "correction" (see Methods), the values were 0 to 275 ms (mean 155 ± 68) in the donor and 119 to 273 ms (mean 177 ± 48) in the recipient (Tables 2 and 3). The four patients with abnormal donor sinus node recovery times had sinoatrial conduction times of 220, 206, 460 and 5 ms, respectively. In the patient with a markedly prolonged conduction time (460 ms), this was primarily due to sinus node suppression but even after "correction", the conduction time was still prolonged (275 ms). Only one patient with a normal donor recovery time had an abnormal sinoatrial conduction time. Of the six patients with abnormal recipient sinus node recovery times, only two had prolonged sinoatrial conduction times. Two of the four patients with normal recovery times, however, had abnormal conduction times.

Sinoatrial node response curve. This was classic in 12 of the 14 donor atria with perfectly flat plateaus during the zone of reset. In the remaining two patients, one had marked sinus node suppression during the zone of reset but not during the zone of nonreset and one had an extremely short conduction time. In the recipient atria, the zones of the curves were less well defined with marked modulation of the A_2-A_3 intervals during the apparent plateau zones.

Comparison of techniques of measuring sinoatrial conduction time. In six donor atria and four recipient atria, the two techniques of measuring sinoatrial conduction times (Strauss [31,32] and Narula [39]) were compared. In the donor atria, there was a very close correlation between the two methods whether the longest ($r = 0.977$, $p < 0.001$) or mean ($r = 0.978$, $p < 0.001$) value for Narula's method was used. In both instances, the slope of the regression line was close to 1 and the intercept close to zero (Fig. 6 and 7). After correction of the Strauss method, the correlation with Narula's method was still good, although less significant (longest: $r = 0.841$, $p < 0.05$; mean: $r = 0.844$, $p < 0.05$). The values obtained after correction tended to be shorter than the values obtained using Narula's method. The correlation between the values obtained by the two techniques in the recipient atria was not significant, although obviously the number of patients is small. The overall results of this study are given in Table 2 and the individual patient results in Table 3.

Discussion

Autonomic nervous system and sinus node function. Normal sinus node function is dependent on a complex balance between intrinsic sinus node electrophysiologic properties, sinoatrial conduction properties and a number of extrinsic factors, the most important of which is the autonomic nervous system (13,43,44). Alterations in auto-

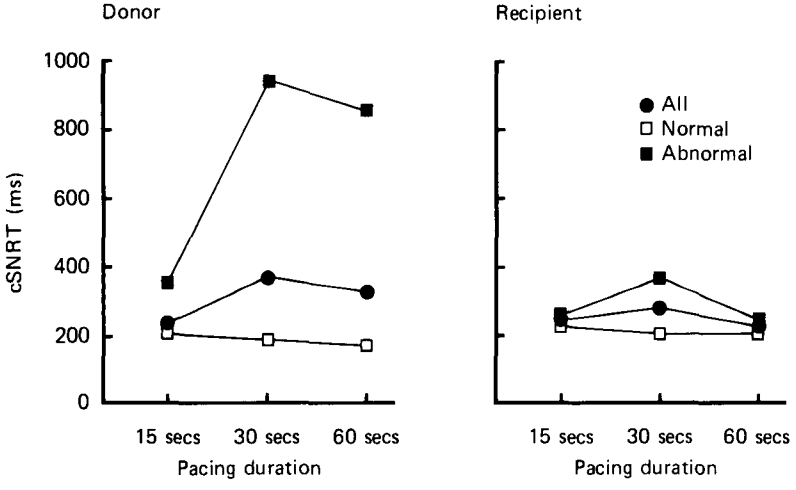


Figure 3. Effect of pacing duration on corrected sinus node recovery time (cSNRT) in the donor and recipient atria. The mean values for each pacing duration are illustrated for all patients, patients with normal sinus node function tests and patients with abnormal tests.

Table 4. Comparison of Heart Rate at Rest of the Donor Atrium With the Calculated Range of Intrinsic Heart Rate From the Age of the Donor Heart Using the Formula of Jose and Collison (41)

Case	Donor HR (beats/min)	Calculated IHR (±2 SD) (beats/min)	Abnormal SNRT
2	66	91 to 121	Yes
3	103	92 to 122	No
4	115	91 to 120	No
6	91	94 to 124	No
10	112	92 to 122	No
12	115	94 to 124	No
13	91	93 to 124	No
16	116	93 to 123	No
17	103	91 to 121	No
18	105	89 to 118	No
19	87	87 to 116	No
20	76	89 to 118	Yes
22	58	92 to 122	Yes
29	85	93 to 123	Yes

HR = heart rate; IHR = intrinsic heart rate; SD = standard deviation; SNRT = sinus node recovery time.

nomic tone may produce the electrocardiographic manifestations of sinus node dysfunction in a basically electrophysiologically normal sinus node and, similarly, may mask the dysfunction of an intrinsically abnormal node (21). The limitations of formal electrophysiologic testing of sinus node function and its failure to discriminate between patients with normal and abnormal sinus node function have been well reported (14,15,34,35,37,45,46). The autonomic nervous system has been implicated as a major source of error in such testing.

In an attempt to overcome this problem, autonomic blockade using the technique of Jose (16), has been used to determine "intrinsic" sinus node function (17–21) with an apparent increase in the sensitivity of sinus node testing. However, as already indicated, this technique may have certain inherent methodologic problems. The denervated state of the donor atria in transplant patients allows the assessment of intrinsic sinus node function in an environment free of pharmacologic agents. Although the donor sinus node is anatomically denervated, it can of course still respond to circulating catecholamines and other neurohormonal substances. In all cases in this study, there was no significant change in donor heart rate at rest throughout the period of the electrophysiologic investigation, suggesting that circulating catecholamines had not materially influenced the results obtained.

Intrinsic heart rate. In those patients with normal sinus node function, the sinus cycle length, sinus node recovery time and corrected recovery time were significantly shorter in the donor atria as would be expected from studies using autonomic blockade (17–21). In the patients with normal donor sinus node function, heart rate at rest fell within, or extremely close to, the expected range of intrinsic heart rate calculated for individual patients from the age of their donor heart. In the patients with abnormal sinus node function, the heart rate at rest was significantly lower than the expected intrinsic rate (Table 4). Previous studies in normally innervated patients (17,19,21) have indicated that there is a strong correlation between abnormal intrinsic heart rate and intrinsic sinus node dysfunction. It could be argued that the range of values indicating abnormal sinus node function after denervation may be considerably different from those currently accepted for the innervated heart. However, even if the normal values for sinus node recovery times after autonomic blockade (Reference 18: upper limit of normal for corrected sinus node recovery time = 505 ms) are used for the donor atria, the number of patients with abnormal results and the relevance of these results remain the same.

Sinus node automaticity. *Effect of increasing pacing rate.* There were marked differences in the response of the innervated and denervated sinus nodes to increasing pacing rate and duration. The recovery time of the donor sinus node

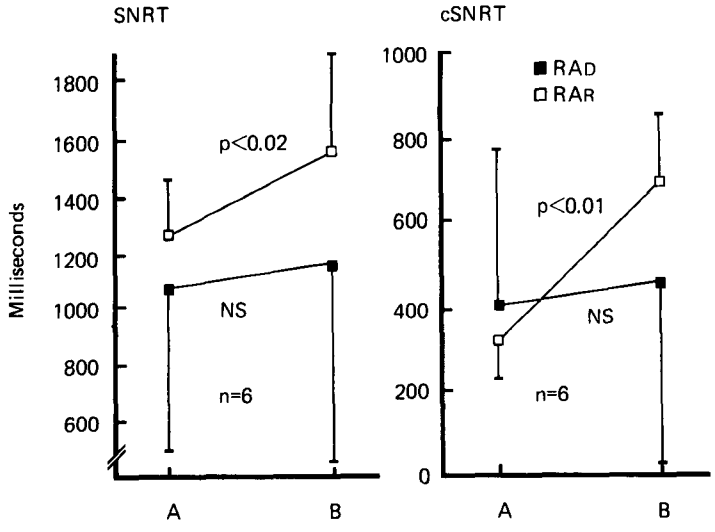


Figure 4. Comparison of the effect of synchronous pacing of both donor and recipient atria (B) with pacing of the respective atrium alone (A) on the recovery times and corrected recovery times of the donor and recipient sinus nodes. The mean values ± 1 standard deviation are indicated. n = number of patients; NS = not significant; other abbreviations as before.

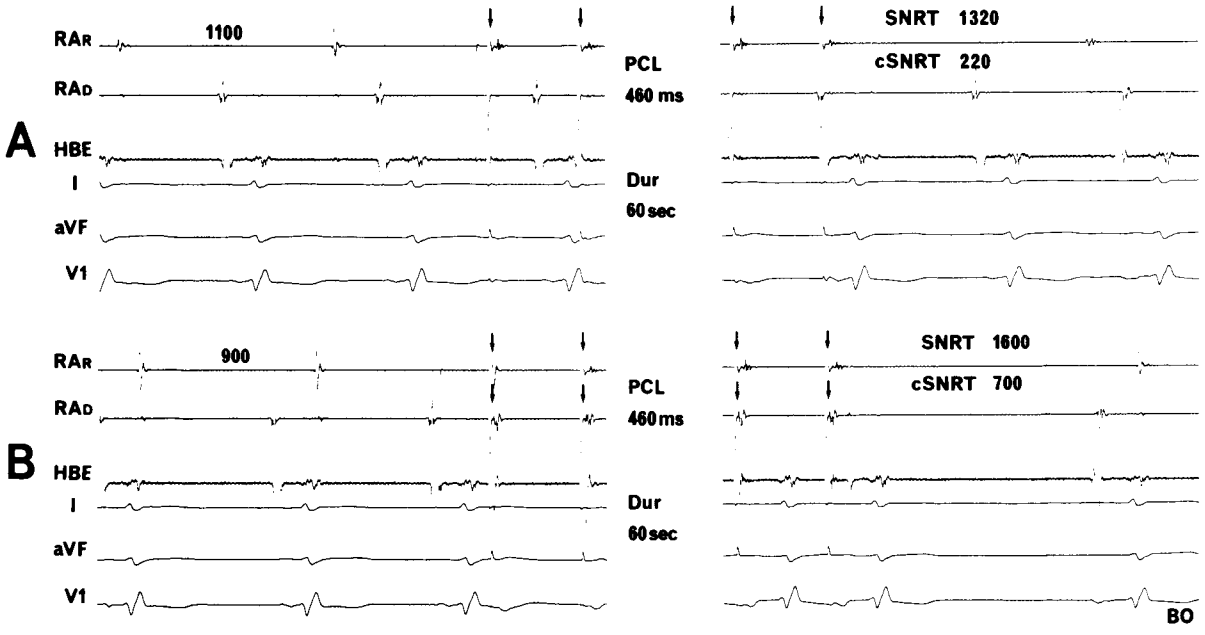
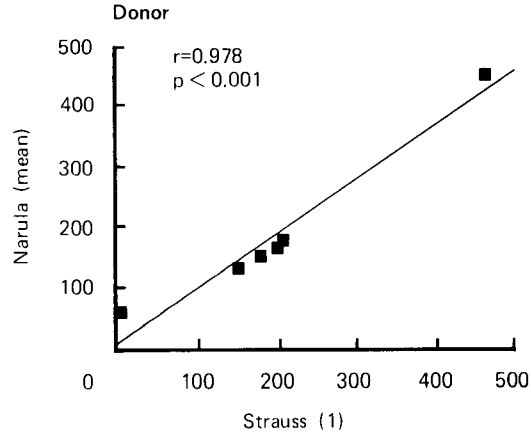


Figure 5. Typical example of the effect of synchronous pacing on the corrected recovery time (cSNRT) of the recipient sinus node. The **upper panel (A)** is recorded during pacing of the recipient atrium alone and the **lower panel (B)** during synchronous pacing of the donor and recipient atria. The **arrows** indicate the pacing stimuli. All values are in milliseconds. Dur = duration; HBE = His bundle electrogram; PCL = pacing cycle length; RA_D = donor right atrial electrogram; RA_R = recipient right atrial electrogram; I, aVF and V_1 are surface electrocardiographic leads; other abbreviations as before.

increased in a predictable and organized manner with increasing pacing rate, and the longest recovery time tended to occur at the shortest pacing cycle length. A similar pattern of response was observed by Mason (11), who reported that the response of the donor sinus node to increasing pacing rate was "organized" in 72% of pacing sequences in a group of transplant patients without overt sinus node dysfunction. Previous studies in both normally innervated patients (27,47) and animals (48–50) have indicated that recovery time tends to increase with increasing pacing rates, but that the trend is reversed at higher rates. In patients, the maximal sinus pause tends to occur at drive rates of 110 to 130 beats/min (27,47). The shortening of recovery time that normally occurs at faster pacing rates may be related to reflex sympathetic discharge as a result of the hemodynamic consequences of pacing (51,52) or to the development of atriosinus block (32,50). Reflex sympathetic nervous changes would obviously have no effect on the denervated sinus node. Also withdrawal of vagal input to the atrial tissue may improve conduction across the perinodal region (11,53), thus preventing the development of atriosinus block and allowing a greater transmission of impulses into the sinus node at the faster pacing rates. In the patients in this study with abnormal donor sinus nodes, although the relation was less predictable, the trend was similar. All of these patients had abnormalities of sinoatrial conduction and, thus, the less predictable relation may have been related to the development of variable sinus node entrance block at the differing pacing rates. In the recipient atria, the relation was similar to that previously reported in normally innervated patients (27,47) with a tendency to shorten at faster pacing rates.

Effect of increasing pacing duration. Similarly, previous studies have demonstrated that the duration of pacing nor-

Figure 6. Correlation between the sinoatrial conduction times measured by the extrastimulus technique (Strauss) and the continuous pacing technique (Narula) in the donor atria. The mean Narula values are plotted against the uncorrected values determined by the Strauss method. The intercept is close to zero (9.36) and the slope close to 1 (0.91). All values are in milliseconds.



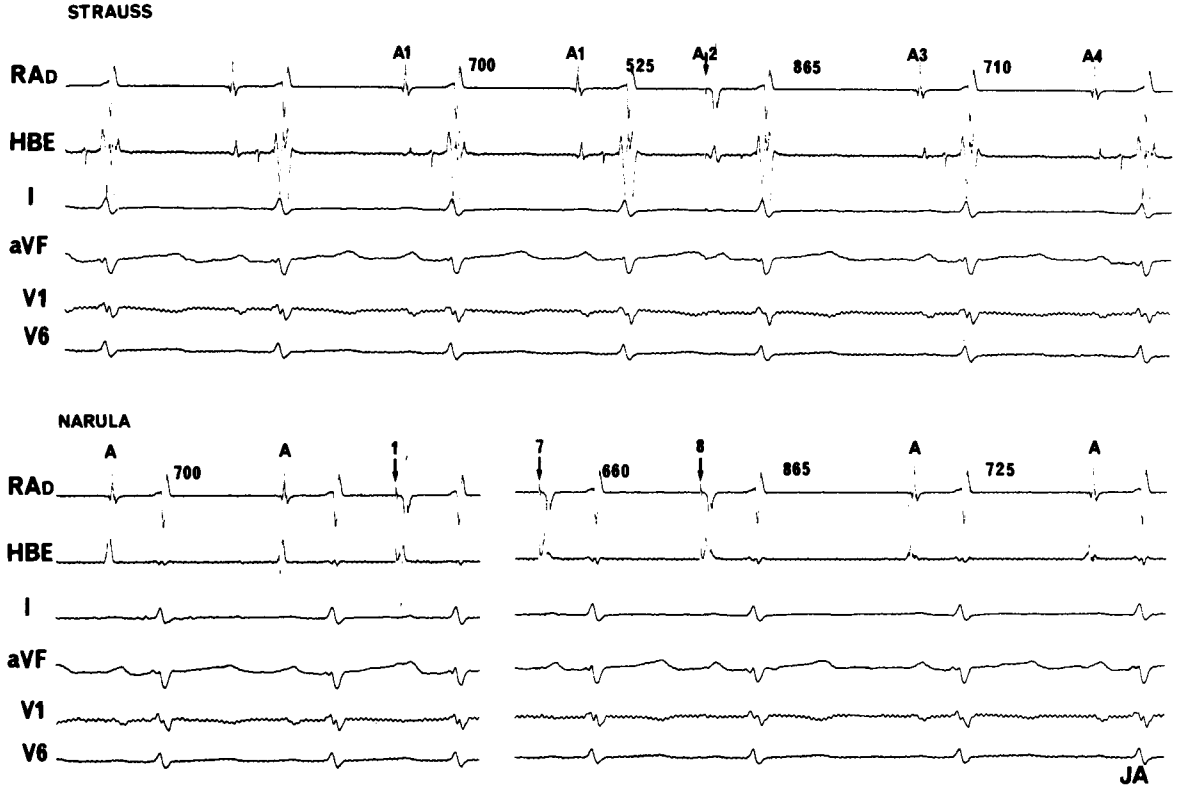


Figure 7. Electrocardiographic recordings during electrophysiologic study demonstrating the correlation between the donor sinoatrial conduction times measured by the techniques of Strauss (**upper panel**) and Narula (**lower panel**) in an individual patient. All values are in milliseconds. Strauss method: A_1-A_1 = cycle length at rest; A_1-A_2 = extrastimulus coupling interval; A_2-A_3 = post extrastimulus pause; A_3-A_4 = first return cycle. Narula method: A-A = cycle length at rest; 1,7,8 = the first, seventh and eighth paced beats of the pacing sequence. HBE = His bundle electrogram; RAD = donor right atrial electrogram; I, aVF, V_1 and V_6 are surface electrocardiographic leads.

mally has little effect on recovery times (27,29,54) apart from slight shortening with longer durations (49). This was also true in the recipient and normal donor sinus nodes in this study. However, in the abnormal donor sinus nodes, increasing pacing duration was associated with longer recovery times. In one study (29) in patients with sinus node dysfunction, in whom the response to autonomic maneuvers may be unpredictable, the recovery time was directly proportional to the rate and duration of pacing.

Secondary pauses. These have been said to be a sensitive index of sinus node dysfunction (45), particularly after autonomic blockade (19). In the present study, there was an absolute correlation between the presence of secondary pauses and abnormal sinus node function in the donor but not in the recipient atria. The prolongation in the donor atria was always less than a whole number multiple of the expected cycle length and, thus, could have resulted from either a disturbance of conduction or automaticity. The four patients demonstrating secondary pauses in the donor atria all had abnormalities of both sinus node recovery and sinoatrial conduction, although the prolongation tended to be sustained and the recovery gradual suggesting a depression of automaticity. In innervated atria, secondary pauses may occur as a consequence of fluctuating autonomic tone resulting from the hemodynamic effects of rapid pacing, even in patients with normal intrinsic sinus node function. In the previous study of Mason (11), although secondary pauses occurred more frequently in the recipient than in the donor atria, no attempt was made to correlate these findings with other indexes of sinus node dysfunction.

Effect of synchronous pacing. The marked effect of extrinsic factors on sinus node function is exemplified by the effect of synchronous pacing on donor and recipient recovery times. Synchronous pacing had little or no effect on donor recovery times. Although the recipient atrial remnants are small, they have been shown to affect left ventricular end-diastolic pressure, peak ventricular pressure and arterial systolic pressure when their contraction is simultaneous with that of the donor atria (6). However, any alteration in hemodynamic status and consequently autonomic tone will have no reflex effect on the denervated sinus node. Synchronous pacing, however, significantly increased the recovery times of the recipient sinus node.

Various theories can be suggested to account for this phenomenon. First, pacing of the recipient atria alone will have no hemodynamic consequences, whereas synchronous

pacing with the donor heart will produce hemodynamic alterations that, at lower rates, will result in increased vagal activity and decreased sympathetic activity, which tend to lengthen recovery times. At faster pacing rates, however, deleterious hemodynamic changes may occur that will tend to reverse these autonomic changes and, thus, shorten recovery times. This is consistent with the fact that the more marked effect of synchronous pacing occurred at the slower pacing rates. Second, during synchronous pacing the donor sinus node is also suppressed, whereas during pacing of the recipient alone donor sinus beats will occur during the recovery period of the recipient sinus node. These may induce recipient sinus node activity through either mechanical (55) or neuronal (56) mechanisms.

Sinoatrial conduction. As with assessment of sinus node automaticity by overdrive suppression, the assessment of sinoatrial conduction time by the extrastimulus technique produced organized and predictable responses in the donor atria. All patients had perfectly flat plateau zones with little or no modulation and sharp transitions from the zone of nonreset to the zone of reset. Although the limitations of the technique have been widely reported (34,35,37,38,57), in this study there was a close association between abnormalities of sinus node recovery and sinoatrial conduction in the donor atria. This was not true in the recipient atria as has been reported in normally innervated hearts (15). One of the major problems in the estimation of sinoatrial conduction by the extrastimulus technique is the presence of sinus arrhythmia (58), which is absent in the donor atria. The striking differences in the donor and recipient sinoatrial conduction curves seen in this study strongly implicate the autonomic nervous system as being responsible for perturbations in the response cycle that frequently occur during testing in the innervated heart.

There was an extremely close correlation between sinoatrial conduction time estimated by the methods of Strauss (31,32) and Narula (39) in the donor atria. One of the purported advantages of the latter method is that it has a negligible effect on sinus node automaticity, thereby reducing errors induced by sinus node suppression (39,57). However, certainly in the denervated atria, the closest correlation occurred with values obtained using Strauss' method uncorrected for sinus node suppression, and after correction the values were generally shorter than those obtained using Narula's method.

Sinus node dysfunction after transplantation. This study has shown that there is a relatively high incidence of sinus node dysfunction in both the donor and recipient atria after transplantation. Although reports from other centers have not specifically delineated their incidence of sinus node dysfunction, it would appear to be less than reported in this study (8). The reason for this discrepancy is not clear because basically the same surgical technique, donor heart preservation and postoperative immunosuppression were used.

The high incidence of recipient sinus node dysfunction may well be related to pre-transplant underlying disease and to the relative ischemia induced by loss of the sinus node artery during the surgical technique. However, dysfunction of the recipient sinus node is of little consequence and is clinically immaterial, except for the fact that it would be unwise to consider use of the recipient node to control "physiologically" the rate of the donor heart. Disease of the donor sinus node is obviously potentially more important. Preliminary studies (26) have suggested that the escape mechanism of the "lower" pacemakers in the denervated heart is unreliable and, therefore, the donor sinus node dysfunction reported here and previously (8) may be associated with the incidence of sudden death in transplant recipients. The relatively high incidence of abnormalities of donor sinoatrial conduction and automaticity may be related to injury of the sinus node during procurement and transportation of the donor heart, to surgical distortion of the atria during the subsequent transplantation procedure or to postoperatively acquired dysfunction as a result of rejection or atherosclerosis.

Implications. The assessment of donor sinus node function of cardiac transplant recipients produces extremely predictable, organized and consistent responses. Abnormalities of sinus node automaticity, as detected by prolonged recovery times and secondary pauses, and of sinoatrial conduction, as detected by the extrastimulus and continuous pacing techniques, correlate well with one another. Patients can be clearly separated into two groups, those with abnormal sinus node function tests and those without. There is little or no overlap between the two groups using standard tests of sinus node function and standard criteria for abnormal values. In the absence of autonomic influences, these investigations would appear to give a good reflection of intrinsic sinus node function. The presence of a "relative bradycardia" in transplant patients is highly suggestive of abnormal sinus node function, although the clinical significance of abnormalities of sinus node function detected during invasive electrophysiologic evaluations in transplant recipients remains to be determined.

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